DETAILED ACTION

Status of Application

The Office mailed a notice of abandonment in this application on 8/12/08. On 9/15/08, applicants filed a petition to revive this application, urging that its abandonment was unavoidable. On 8/13/10, Petitions Attorney Johnson dismissed the petition for being inadequate. On 9/28/10, applicants submitted a renewed petition, this time urging that the abandonment was unintentional. On 1/25/11, Petitions Attorney Johnson granted the renewed petition, and the Office revived the application.

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application on 9/15/08, after the 12/13/07 final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 9/15/08 has been entered.

Claims 1, 2, and 4-35 are pending. Claims 1, 2, 4-14, 16-28, and 30-35 are currently under examination. Claims 15 and 29 remain withdrawn. Applicant's elections without traverse of the species "C_{16}-C_{24} fatty acid esters," "human growth hormone," and "benzyl benzoate" in the 10/31/06 and 1/26/07 replies are still in effect over the claims.

Claim Objections

Claim 18 is objected to because of the following informalities: The claim contains the term "C.sub.16-C.sub.24," which is different from the previously recited claim

language ("C_{16}-C_{24}"). The examiner has declined to send a notice of noncompliant reply, because the status of the claim is not in question. However, future claim listings that do not make note of all changes to the immediately prior claim listing will be held noncompliant. 37 C.F.R. § 1.121(c). Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 2, and 4-14 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 recites the limitation "the hydrophobic agent" at line 3, but there is no antecedent basis for this limitation anywhere in claim 1. Claim 1 recites "an agent exhibiting a characteristic of low solubility in water," not a "hydrophobic agent." Clarification is required. Because claims 2 and 4-14 depend from indefinite claim 1 and do not clarify the point of confusion, they must also be rejected under 35 U.S.C. 112, second paragraph.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 2, 4-14, 16-28, and 30-35 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Brodbeck et al. (2000, U.S. Patent 6,130,200; 5/25/05 IDS) taken in view of Yamagata et al. (1997, U.S. Patent 5,628,993; 5/25/05 IDS) and Ayer et al. (2000, U.S. Patent 6,096,339). Brodbeck is prior art under 35 U.S.C. § 102(e) because the application was filed in the U.S. before the current application and the inventive entity differs from that of the instant application; see M.P.E.P. § 2136.04.

Brodbeck teaches a sustained-release pharmaceutical composition comprising particles of spray-dried, lyophilized human growth hormone (HGH, an active agent that is a water-soluble polypeptide) and zinc acetate (a solubility modulator) suspended in a gel of poly-(D,L-lactide-co-glycolide) (PLGA, a biocompatible gel carrier) and benzyl benzoate (a solvent) (Example 2; column 23, line 45, through column 26, line 16). Brodbeck teaches that the solubility modulator, *i.e.*, an agent that alters the solubility of the active agent with reference to the polymer solvent or water (column 10, lines 17-29), may be a lipid or oil (column 15, lines 39-43, especially line 42). Brodbeck teaches making this composition by mixing a biocompatible polymer with the benzoic acid solvent to form a viscous gel, dispersing an active agent associated with a solubility modulator into the gel, and adding further components as desired (column 6, line 62, through column 7, line 7); specifically, Brodbeck teaches spray-drying a mixture of HGH

and zinc acetate to yield 2-100 micron particles (column 23, line 50, through column 24, line 27).

Brodbeck does not exemplify a composition in which the solubility modulator is hydrophobic, specifically a fatty acid ester, more specifically a C_{16}-C_{24} fatty acid ester, more specifically a mixture of stearic acid and palmitic acid in particular proportions. Brodbeck does not teach making the particles comprising the active agent by crushing a compressed mass of active agent.

Yamagata teaches a sustained-release pharmaceutical composition comprising powdered particles comprising interferon-α (a water-soluble polypeptide) dispersed in a matrix of tetraglycerol dipalmitate (a fatty acid ester of palmitic acid) or tetraglycerol distearate (a fatty acid ester of stearic acid) (Examples 1-3; column 8, lines 3-37; column 6, lines 21-38). The composition of Yamagata may comprise hormones (column 4, lines 25-32). Yamagata teaches that the composition may comprise more than one fatty acid diester (column 5, lines 32-34; column 6, lines 4-5) and that the amount of each fatty acid diester in the composition may be optimized (column 6, lines 39-45).

Ayer teaches that particles comprising active agents that are included in controlled-release pharmaceutical compositions may be made by spray-drying or crushing, among other methods (column 13, lines 15-21).

A person of ordinary skill in the art would have had a reasonable expectation of success in substituting the palmitic acid and stearic acid diesters of Yamagata for the zinc acetate as a solubility modulator in the composition of Brodbeck because Brodbeck suggests that lipids and oils may act as solubility modulators. The skilled artisan would

have been motivated to substitute the diesters of Yamagata for the zinc acetate in the composition of Brodbeck because Yamagata teaches that the diesters protect physiologically active peptides from hydrolysis and preserve their activity, allowing for sustained release of active polypeptide (column 2, lines 14-19).

The selection of the amount of palmitic acid diester and stearic acid diester to include in the composition of Brodbeck would have been a routine matter of optimization on the part of the artisan of ordinary skill, said artisan recognizing that Yamagata teaches that the amount of a given diester in a sustained-release composition is widely optimizable (column 6, lines 39-45). A holding of obviousness over the cited claims is therefore clearly required.

The selection of the method used to make particles comprising HGH and the solubility modulator in the method of Brodbeck would have been a routine matter of optimization on the part of the artisan of ordinary skill, said artisan recognizing that Ayer teaches that spray-drying and crushing are art-accepted equivalents for yielding particles of dried pharmaceuticals, including polypeptides (column 11, lines 37-47, especially line 41). A holding of obviousness over the cited claims is therefore clearly required.

It would therefore have been obvious to a person of ordinary skill in the art at the time the invention was made to substitute various amounts of palmitic acid diester and stearic acid diester for the zinc acetate in the composition of Brodbeck and to substitute crushing for spray-drying in the method of procuction because Yamagata teaches that fatty acid diesters are solubility modulators, because Brodbeck suggests that the

solubility modulator may be a lipid, and because Ayer establishes the art-recognized equivalence of crushing and spray-drying for producing particles of pharmaceutically active agents.

Therefore, the invention as a whole would have been *prima facie* obvious to a person of ordinary skill at the time the invention was made.

Applicant alleges that Brodbeck does not teach a composition comprising a compressed mixture as instantly claimed (Reply at 7.) Applicant alleges that the references do not recognize "the criticality of compression. (Reply at 7-8.) Applicant alleges that the Office has "ignore[d] evidence of the superiority of the recited compressed particles and related methods," referring to Figures 2-4 and page 46 of the specification. These arguments have been fully considered, but they are not persuasive of error.

In response to applicant's arguments against the Brodbeck reference individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). The examiner has conceded that Brodbeck does not teach or exemplify all of the elements of the claimed invention; such is the basis for this rejection under section 103, not section 102.

In response to applicant's argument that the art did not recognize that compression is critical, the fact that applicant has recognized another advantage which would flow naturally from following the suggestion of the prior art cannot be the basis for

patentability when the differences would otherwise be obvious. See *Ex parte Obiaya*, 227 USPQ 58, 60 (Bd. Pat. App. & Inter. 1985). Ayer teaches that compression and spray-drying are equivalents for each other in the art of controlled-release pharmaceutical composition production. The fact that Ayer does not teach that compression is superior in some way is irrelevant. Furthermore, it is not clear for what outcome compression is "critical," it is not clear which of the Office's references are "unit operations," and it is unclear to what genus applicant refers as "the broad genus" at page 8. These remarks are wholly confusing.

The experimental results to which applicants refer at page 8 have no clear relevance to the claims. To be given substantial weight in the determination of obviousness or nonobviousness, evidence of secondary considerations must be relevant to the subject matter as claimed. M.P.E.P. § 716.01(b). There must be a nexus, a "a factually and legally sufficient connection between the objective evidence of nonobviousness and the claimed invention." M.P.E.P. § 716.01(b). Furthermore, when evidence of unexpected results is proffered, applicants bear the burden of explaining the data. M.P.E.P. § 716.02(b), part II. Finally, the evidence must establish that the differences are unexpected, unobvious, and of both practical and statistical significance. M.P.E.P. § 716.02(b), part I. Applicant's reply fails to comply with any of these requirements.

The experiments whose results are shown in Figures 2-4 regard the release of lysozyme from a gel containing PLGA 502 and benzyl benzoate. (Specification at page 45, lines 13-15.) The gel contains 10-20% by weight of particles containing lysozyme

and sucrose and, optionally, particles of stearic acid or palmitic acid. (Specification at page 44, lines 20-22.) The particles have particular sizes. (Specification at page 45, lines 3-6.) The lysozyme particles were made by spray drying. (Specification at page 44, line 20.) The specification also details making HGH particles by spray drying. (Specification at page 44, line 5.) The claims do not include lysozyme at all; they are not limited to compositions containing PLGA 502 and benzyl benzoate; and applicants have made clear that the selection of compression as the manner of making the particles is "critical." The working examples applicants cite bear no clear resemblance to the claims at all.

Even if the claims did include all of the elements taught in the working examples (spray-dried lysozyme, PLGA 502, and benzyl benzoate), the data in the specification does not clearly indicate that there is anything truly unexpected or nonobvious. The art recognized stearic acid and palmitic acid esters as being useful in the production of extended-release compositions (see Yamagata), so the fact that lysozyme is released more slowly when the compositions contain stearic acid and palmitic acid esters is in no way surprising. Applicant's blanket statement at page 8 that "several embodiments of the claimed invention have better release performance as compared to non-inventive examples" does not meet the requirement to clearly explain proffered data. Especially because applicants urge that the selection of compression as the manner in which the particles are made, the data is inadequate to support a finding of nonobviousness, and applicants' remarks do not compel such a conclusion. Applicant has supplied no evidence that the invention as claimed, i.e. across its entire breadth, yields any result

other than what would be expected given the teachings of Brodbeck, Yamagata, and Ayer about the production of sustained-release pharmaceutical compositions.

No claims are allowed. No claims are free of the art.

Applicant is requested to specifically point out the support for any amendments made to the disclosure in response to this Office action, including the claims (MPEP 714.02 and 2163.06). In doing so, applicant is requested to refer to pages and line numbers in the as-filed specification, **not** the published application. Due to the procedure outlined in MPEP § 2163.06 for interpreting claims, it is noted that other art may be applicable under 35 U.S.C. § 102 or 35 U.S.C. § 103(a) once the aforementioned issue(s) is/are addressed.

Applicant is requested to provide a list of all copending U.S. applications that set forth similar subject matter to the present claims and share an inventor or assignee with the instant application. A copy of such copending claims is requested in response to this Office action in order to assist the examiner with double patenting analysis in the application.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lora E. Barnhart whose telephone number is 571-272-1928. The examiner can normally be reached on Monday-Thursday, 9:00am - 5:30pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sue X. Liu, can be reached on 571-272-5539. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Lora E Barnhart/
Primary Examiner, Art Unit 1653